

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Letters Patent of:  
Gentz et al.

Docket No.: PF454P2

Patent No.: 7,285,267

Issued: October 23, 2007

For: Antibodies to Tumor Necrosis Factor Receptors 6  
Alpha & 6 Beta

**LETTER REGARDING CORRECTED PATENT**

ATTN: Delora Dillard  
Certificate of Correction Branch  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

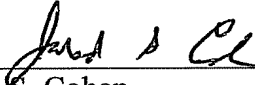
Sir:

Pursuant to telephone conversations between Patentees and Certificate of Corrections Branch staff Rochaun Johnson and Delora Dillard, it is Patentees' understanding that the Request for Corrected Patent filed January 23, 2008 was approved and that a corrected patent will be issued. In response to a request by Ms. Dillard, Patentees submit herewith a properly formatted draft Certificate of Correction for use in verifying the corrections to be made in the republished patent.

Patentees believe that no fee is required for this submission. However, if a fee is required, please charge such fee to our Deposit Account No. 08-3425.

Dated: JUNE 23, 2009

Respectfully submitted,

By   
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**UNITED STATES PATENT AND TRADEMARK OFFICE  
CERTIFICATE OF CORRECTION**

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PATENT NO. : 7,285,267  
APPLICATION NO. : 09/935,727  
ISSUE DATE : October 23, 2007  
INVENTOR(S) : Gentz et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

At Item (54), the Title should read --Antibodies to Tumor Necrosis Factor Receptors 6 $\alpha$  & 6 $\beta$ --.

At Item (56) References Cited-Other Publications, at page 2, column 2, line 13, reference Bai et al., GenBank Accession No. AF217796, delete "Feb. 12, 2000" and insert therefor --Feb. 21, 2000--.

At Item (57) Abstract, line 4, delete "polypeptides are also" and insert therefor --polypeptides and antibodies that bind TNFR-6 $\alpha$  & 6 $\beta$  polypeptides are also--.

In the Specification:

At column 1, line 38, delete "TNFR-6 $\alpha$  & TNFR-6 $\beta$ " and insert therefor --TNFR-6 $\alpha$ , & TNFR-6 $\beta$ --.

At column 1, lines 41-42, delete "The invention further relates to screening" and insert therefor --The invention further relates to screening methods for identifying agonists and antagonists of TNFR polypeptide activity. Also provided are diagnostic and therapeutic methods utilizing such compositions.--.

At column 3, line 49, delete "FIGS. 1 and 2" and insert therefor --FIGS. 1 and 2A-B--.

At column 3, line 59, delete "miRNAs for TNFR-I and -II (FIG. 3)" and insert therefor --mRNAs for TNFR-I and -II (FIGS. 3A-P)--.

At column 3, lines 65-66, delete "FIGS. 1 and 2" and insert therefor --FIGS. 1 and 2A-B--.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 5, line 1, delete "has has" and insert --has--.

At column 6, line 43, delete "FIG. 2 shows" and insert --FIGS. 2A-B show--.

At column 6, line 47, delete "FIG. 3 shows" and insert --FIGS. 3A-P show--.

At column 7, line 21, delete "(FIG. 2)" and insert --(FIG. 2A)--.

At column 7, line 23, delete "(FIG. 2)" and insert --(FIG. 2A)--.

At column 7, lines 45-46, delete "Fas ligand" and insert --Fas-Fc--.

At column 7, line 56, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 8, line 3, delete "(FIG. 3)" and insert --(FIGS. 3A-P)--.

At column 8, line 45, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 8, line 50, delete "(FIGS. 1 and 2" and insert --(FIGS. 1 and 2A-B--.

At column 8, line 55, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 8, line 59, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 9, line 6, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 11, lines 40-41, delete "FIG.1 or 2" and insert --FIG.1 or 2A-B--.

At column 12, line 10, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 12, line 20, delete "FIGS.1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 12, lines 27-28, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At column 13, line 24, delete "13000," and insert --1300, --.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

- At column 16, line 7, delete "FIG. 2" and insert --FIG. 2A--.
- At column 16, line 17, delete "TNFR-6□" and insert --TNFR-6α--.
- At column 16, line 22, delete "TNFR-6□" and insert --TNFR-6α and/or TNFR-6β--.
- At column 29, line 12, delete "FIG. 2" and insert --FIGS. 2A-B--.
- At column 29, line 31, delete "FIG. 2" and insert --FIGS. 2A-B--.
- At column 30, line 13, delete "MRNA" and insert --mRNA--.
- At column 32, line 29, delete "FIG. 2" and insert --FIGS. 2A-B--.
- At column 32, line 53, delete "FIG. 2" and insert --FIGS. 2A-B--.
- At column 36, line 8, delete "NSO)" and insert --NS0)--.
- At column 37, line 9, delete "pHN-4-5" and insert --pHE4-5--.
- At column 38, line 31, delete "CK-□8" and insert --CK-β8--.
- At column 43, line 42, delete "detecable" and insert --detectable--.
- At column 48, line 66, delete "encoding a "FLAG" polypeptide. Thus, a" and insert --encoding a FLAG® polypeptide (DYKDDDDK). Thus, a--.
- At column 49, line 1, delete "FLAG" and insert --FLAG@--.
- At column 49, line 6, delete "pFLAG-CMV-5a or a pFLAG-CMV-1" and insert --pFLAG-CMV™-5a or a pFLAG-CMV™-1--.
- At column 49, line 13, delete "anti-FLAG" and insert --anti-FLAG@--.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 50, line 4, delete "FIG. 2" and insert --FIG. 2A--.  
At column 50, line 15, delete "FIG. 2" and insert --FIG. 2A--.  
At column 53, line 43, delete "85:5409" and insert --85:5409-5413 (1988)--  
At column 55, line 19, delete "flag" and insert --FLAG@--.  
At column 55, line 60, delete "TNF-alph," and insert --TNF-alpha--.  
At column 56, line 22, delete "are include" and insert --include--.  
At column 57, line 34, delete "FIG. 2" and insert --FIG. 2A--.  
At column 64, line 26, delete "FIG. 2" and insert --FIG. 2A--.  
At column 64, line 31, delete "FIG. 2" and insert --FIG. 2A--.  
At column 64, line 33, delete "FIG. 2" and insert --FIG. 2A--.  
At column 65, line 14, delete "FIG. 2" and insert --FIG. 2A--.  
At column 65, line 41, delete "FIG. 2" and insert --FIG. 2A--.  
At column 65, line 45, delete "FIG. 2 (i.e., SEQ ID NO:2)" and insert --FIG. 2A (i.e., SEQ ID NO:4)--.  
At column 65, line 47, delete "FIG. 2" and insert --FIG. 2A--.  
At column 66, line 24, delete "FIG. 2" and insert --FIG. 2A--.  
At column 66, line 31, delete "FIG. 2" and insert --FIG. 2A--.  
At column 87, line 63, delete "and the "flag" tag." and insert --and the FLAG@ tag--.  
At column 125, line 43, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

- At column 127, line 11, delete "FIG. 2" and insert --FIGS. 2A-B--.
- At column 127, lines 63-64, delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.
- At column 151, line 23, delete "anti-FLAG" and insert --anti-FLAG®--.
- At column 151, line 26, delete "anti-FLAG" and insert --anti-FLAG®--.
- At column 154, line, 60, delete "FLAG" and insert --FLAG®--.
- At column 154, line 62, delete "Flag" and insert --FLAG®--.
- At column 154, line 64, delete "Flag" and insert --anti-FLAG®--.
- At column 154, line 66, delete "anti-Flag" and insert --anti-FLAG®--.
- At column 155, line 2, delete "anti-Flag" and insert --anti-FLAG®--.
- At column 155, lines 9-10, delete "(Table IV). Treatment" and insert --(Table V). Treatment--.
- At column 155, line 39, delete "anti-FLAG (200 ng/ml)" and insert --anti-FLAG® antibody (200 ng/ml)--.
- At column 155, line 42, delete "anti-FLAG Mab" and insert --anti-FLAG® antibody Mab--.
- At column 165, lines 42-44 delete the subheading "Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models Diabetic Db+/Db+ Mouse Model" and insert the following two subheadings:
  - Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models*
  - A. Diabetic db+/db+ Mouse Model--.*

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 174, line 40, delete "FLAG-FasL+FLAG antibody" and insert --FLAG-FasL+anti-FLAG® antibody--.

At column 174, line 43, delete "its FLAG domain" and insert --its FLAG® domain--.

At column 174, line 45, delete "the FLAG antibody" and insert --the anti-FLAG® antibody--.

At column 174, line 56, delete "anti-FLAG mouse" and insert --anti-FLAG® mouse--.

At column 174, line 59, delete "and anti-FLAG" and insert --and anti-FLAG®--.

At column 175, line 7, delete "with FLAG" and insert --with anti-FLAG®--.

At column 175, delete the paragraphs beginning at line 22 ("BIAcore Analysis of TR6-Fc...") and ending at line 42 ("...the presence of TR6-Fc or Fas-Fc.") and insert the following subheadings and paragraphs:

-- *BIAcore Analysis of TR6-Fc Binding to FasL*

BIAcore chip technology provides the opportunity to identify and characterize ligands that bind to a given receptor, in this case TR6. The protein ligand can be immobilized and challenged with TR6 to calculate relative binding units (RU). Conversely, the TR6 receptor can be immobilized and exposed to various ligands to identify proteins with an affinity for the TR6 receptor.

BIAcore technology was used to determine if human TR6-Fc displayed any binding to human FasL immobilized on a BIAcore chip. The results indicated that TR6-Fc bound to FasL with the same affinity as the Fas receptor, approximately 100 RU. As a control, TR6-Fc interaction with another ligand, BLyS, was examined. No significant binding was found.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

To show the specificity of TR6-Fc for FasL, soluble FLAG-FasL was used to compete with the immobilized FasL for binding of TR6-Fc. Increasing concentrations of FasL-Flag were able to inhibit binding of TR6-Fc to immobilized FasL. At a concentration of 8 ug/ml, FasL-Flag inhibited binding of TR6-Fc \*2 ug/ml by 50 percent. When 17 ug/ml of Fas-Flag was used, inhibition rose to 75 percent.

When TR6-Fc was immobilized, and trimerized FLAG-FasL used as the soluble protein, the Kd of TR6-Fc was  $4.6 \times 10^{-9}$  M, similar to the  $7.4 \times 10^{-9}$  M Kd for FasFc. TR6 without the Fc portion had a fourfold reduction in affinity for FasL-Flag with a Kd of  $1.7 \times 10^{-8}$  M.

*In vitro effect of TR6 on soluble human FasL mediated cytotoxicity*

The results of this experiment demonstrate the ability of TR6 to block cross-linked FLAG-FasL mediated HT-29 cell death. FLAG-FasL induced HT-29 cytotoxicity in a dose-dependent manner, with a maximal effect at a concentration between 1 and 10 ng/ml. In the presence of TR6-Fc (1 ug/ml), FasL failed to induce cell killing, in agreement with the proposed decoy receptor function of TR6. Unlike TR6-Fc, Fas-Fc did not totally abrogate FLAG-FasL mediated cell death, but did shift the cytotoxicity curve about 10 fold to the right. TR6-non-Fc also inhibited FasL mediated killing, but was not as potent as the Fc fusion protein. A number of other members of the TNF receptor family, such as TNFR1-Fc, LTBR-Fc, TR2-Fc, TR4-Fc, TR7-Fc, TR8-Fc, TR9-Fc, TR10-Fc and TR11-Fc were also tested in this assay and failed to block FasL induced killing of HT-29 cells. In a different cytotoxicity assay involving the eponymous TNF family member, TR6-Fc failed to inhibit TNFa-induced killing of L929 target cells.

The ability of TR6 to block antibody cross-linked FLAG-FasL killing *in vitro* was also observed using human Jurkat cells in a similar cytotoxicity assay. Treatment with FasL at 10 ng/ml resulted in an 80% decrease in cell viability as measured by fluorescence at 530/590. Fas-Fc as well as TR6-Fc and non-Fc significantly reduced FasL-induced cytotoxicity whether the decoy receptor level was kept constant and FasL increased, or the FasL level kept constant and the decoy receptor increased. In both assay systems TR6-Fc appeared to be at least 100 fold more potent than Fas-Fc.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In another Jurkat cell assay, treatment with FLAG-FasL resulted in an approximate 7-fold increase in the number of apoptotic cells over untreated controls, as measured by FACS analysis of annexin staining. FasL-mediated apoptosis was significantly reduced in a dose dependant fashion in the presence of TR6-Fc or Fas-Fc.--

At column 176, line 4, delete "by FLAG" and insert --by anti-FLAG®--.

At column 176, lines 12-13, delete "of FLAG antibody" and insert --of anti-FLAG® antibody--.

At column 176, line 22, delete "FLAG antibody" and insert --anti-FLAG® antibody--.

At column 176, lines 29-30, delete "of FLAG antibody (Table V). This" and insert --of anti-FLAG® antibody (Table VII). This--.

Delete the paragraphs and table spanning column 176, line 45 to column 177, line 16, and insert the following paragraphs and tables:

--To determine if TR6-Fc exhibited protective activity when injected sc, as opposed to iv, 350 ug of TR6-Fc was injected sc, 1.5, 3 or 5 hours before iv injection of 4 ug of FLAG-FasL mixed with 15 ug of anti-FLAG® antibody (Table VIII). Even at the receptor:ligand molar ratio of 27:1, none of the animals injected sc with TR6-Fc survived for more than two hours, while all of the animals injected iv with 93 ug of TR6-Fc or Fas-Fc survived. A different member of the TNF receptor superfamily, TR-11 (93 ug/mouse, iv) was used as a negative control, and failed to protect any animals from FLAG-FasL induced death. Analysis of blood drawn from mice, injected iv with TR-6-Fc + FasL showed no significant elevation of AST or ALT levels compared to normal controls.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

**Table VII. Dose dependant effect of TR6-Fc (iv) on cross-linked FLAG-FasL induced mortality**

Groups (n=10) (ug/mouse)	Time/% Survival				
	< 2 Hrs	< 4 Hrs	1 Day	4 Days	7 Days
Normal	100	100	100	100	100
FLAG-FasL (3) + anti-FLAG® Ab (12)	10	10	10	10	10
FasL + Ab + TR6-Fc (2)	0	0	0	0	0
FasL + Ab + TR6-Fc (8)	100	10	10	10	10
FasL + Ab + TR6-Fc (24)	90	80	80	70	70

TR6-Fc and/or FLAG-FasL + anti-FLAG® antibody was injected iv into female Balb/c mice as described in the Material and Methods.

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It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

**Table VIII. Effect of TR6-Fc (sc, iv) and Fas-Fc (iv) on cross-linked FLAG-FasL induced mortality**

Groups	Time/% Survival	
	< 2 Hours	> 24 Hours
Normal	100	100
FLAG-FasL (4µg/mouse) + anti-FLAG® Ab (15 µg/mouse)	0	0
TR6Fc (350µg/mouse) sc, -5 hr	0	0
TR6Fc (350µg/mouse) sc, -3 hr	0	0
TR6Fc (350µg/mouse) sc, -1.5 hr	0	0
TR6Fc (93µg/mouse) iv, -1 hr	100	100
Fas-Fc (93µg/mouse) iv, -1 hr	100	100
TR11-Fc (93µg/mouse) iv, -1 hr	0	0

All groups except normal controls received an iv injection of FLAG-FasL + anti-FLAG® antibody at Time 0.--

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At column 182, line 26, delete "H-2<sup>bxd</sup> F1 mice" and insert --H-2<sup>bxd</sup> F1 mice--.  
At column 187, line 1, delete "testeddid" and insert --tested did--.  
At column 188, line 14, delete "FLAG tag)" and insert --FLAG® tag)--.  
At column 189, line 64, delete "pFLAGCMV1" and insert --pFLAG-CMV™1--.  
At column 191, line 11, delete "anti-FLAG M2" and insert --anti-FLAG® M2--.  
At column 191, line 52, delete "anti-FLAG M2" and insert --anti-FLAG® M2--.  
At column 196, line 52, delete "(see FIG. 3)".  
At column 196, line 54, delete "; FIG. 3".  
At column 196, line 67, delete "(Table 1)" and insert --(Table IX)--.  
At column 197, line 1, delete "Table 1" and insert --Table IX--.

**In the Claims:**

At column 248, claim 19(d), line 19, delete "residues the" and insert --residues of the--.

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